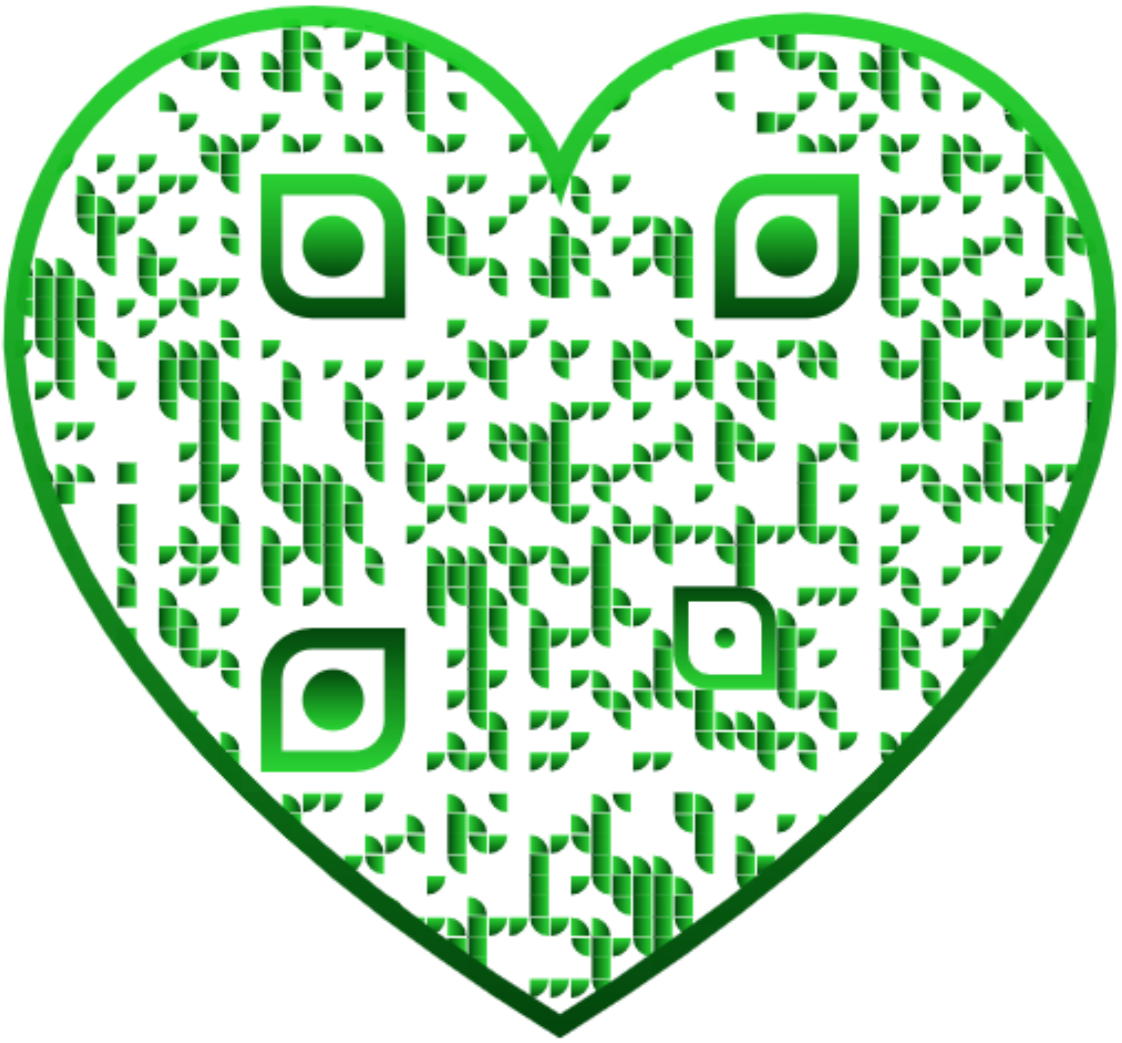
Part two
Clinical Pharmacokinetics



1. Introduction

- **Definitions**
- **Applications of Pharmacokinetics**
- **PK and PD relationships**
- **Some important terms in Pharmacokinetics**

Introduction

- To achieve optimal therapy, the appropriate "**drug of choice**" must be selected.
- This decision implies:
  - An accurate diagnosis of the disease
  - Knowledge of the clinical state of the patient, and
  - Pharmacotherapeutic management of the disease

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- And, the questions **How much?** **How often?** and **How long?** of the drug must be answered.
- In the past, the answers for such questions were obtained by trial and error.
- *In vitro* and *in vivo* studies show that the magnitude of the response is a function of the concentration of drug in the fluid bathing the site(s) of action.

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- The therapeutic objective can be achieved by maintaining an adequate concentration of drug at the site(s) of action for the duration of therapy.

- A drug must therefore move from the site of administration to the site of action.

- Adequate drug administration requires knowledge of - the mechanisms of **ADME**, and the **kinetics** of these processes.

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- **Kinetics** - is the study dealing with the rate of chemical and physical reactions.
  - Kinetics of a substance in a biological system is its spatial and temporal distribution in that system.
  - Includes - entry into the system, subsequent distribution, transport into and from cells, and elimination.
  - Together these events characterize the substance and the system in which it resides.

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- **Pharmacokinetics** (PK) provides a mathematical basis to assess the time course of drugs and their effects in the body.
  - It enables the Absorption, Distribution, Metabolism, Excretion (ADME) processes to be quantified.
    - i.e. is the kinetic study of the time course of drug ADME

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- PK also concerns the relationship of these processes to the **intensity** and **time** course of pharmacologic effects of drugs.
- PK is a fundamental scientific discipline that underpins **applied therapeutics**.
- The design of a dosage regimen is dependent on a basic understanding of the drug use process.

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- A Pharmacist in a clinical practice needs to identify:
  - Need for a drug
  - Choice of a drug
  - Goals of therapy
  - Design of regimen: Route, Dose and Frequency, Duration, Monitoring and Review
  - Counselling

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- The pharmacist needs to ensure that:
  - The appropriate regimen is prescribed to achieve optimal efficacy and minimal toxicity.
  - The appropriate monitoring is undertaken.
  - The patient receives the appropriate information to ensure compliance.
- The application of PK principles to the safe and effective therapeutic management of drugs in an individual patient is **clinical pharmacokinetics**.

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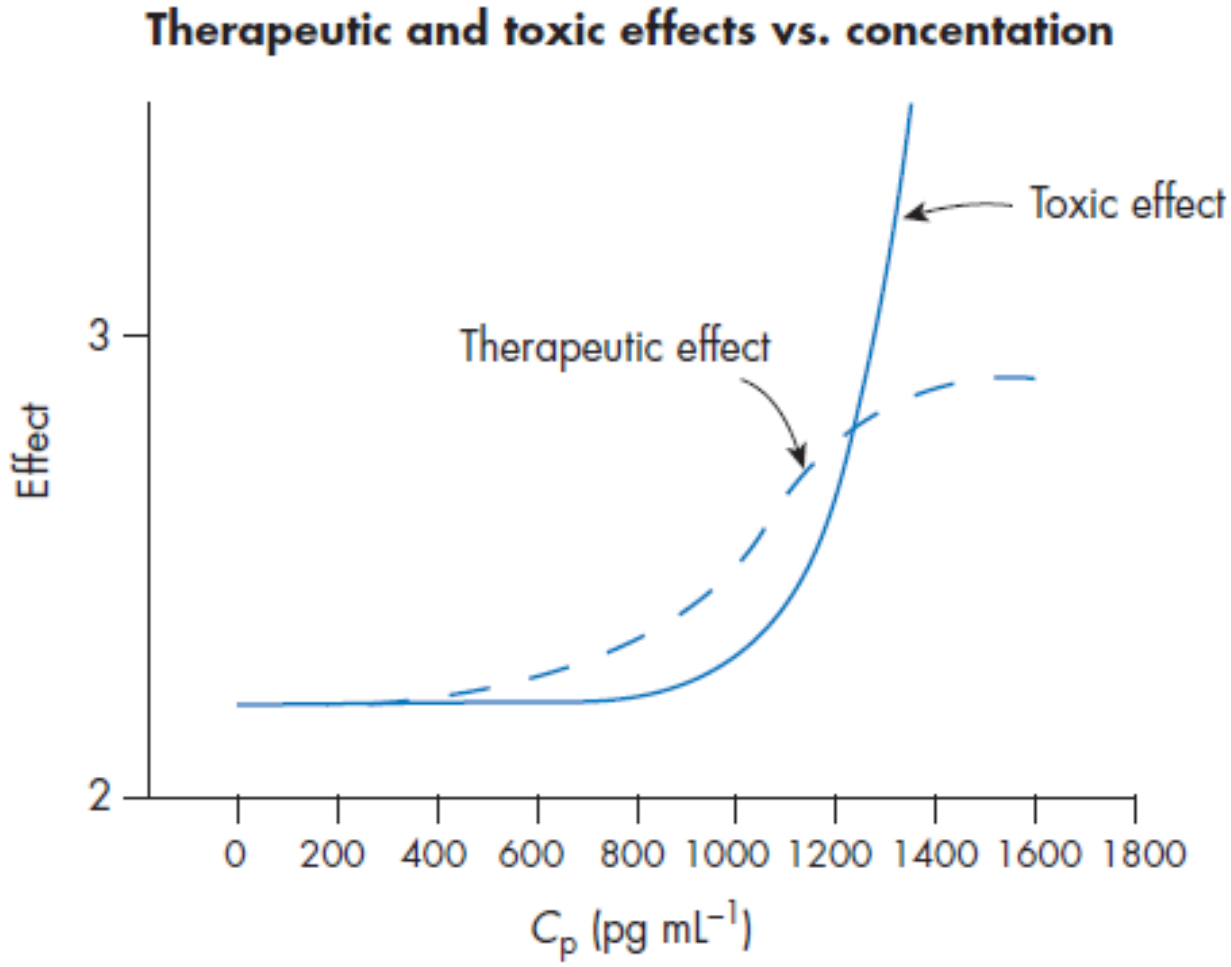
- **Applications of pharmacokinetic studies:**
  - Bioavailability measurements.
  - Effects of physiological and pathological conditions on drug disposition and absorption.
  - Dosage adjustment of drugs in disease states, if and when necessary.
  - Correlation of pharmacological responses with administered doses.
  - Evaluation of drug interactions.
  - Clinical prediction: using PK parameters to individualize the drug dosing regimen and thus provide the most effective drug therapy.

Pharmacodynamics

- PD is the study of biological and therapeutic effects of the drug (drug effect on the body).
- It is a major concern of pharmacology.

PK - PD relationships

- PK describes what the body does to the drug (ADME); while PD measures what the drug does to the body (therapeutic and/or toxic effect).
- For most drugs, there is a **correlation** between drug response and drug concentration in the plasma.
- This correlation is **not**, however, a **linear** one.
    - In fact, for most drugs, a sigmoidal (S-shaped) relationship exists between these two factors.


Therapeutic and toxic effects vs. concentation
Toxic effect
Therapeutic effect
Effect
3
2
0
200
400
600
800
1000
1200
1400
1600
1800
C_p (pg mL^{-1})

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- The best measure of a drug's activity would be obtained from a direct and quantitative measurement of the drug's therapeutic effect.
  - This is, in fact, possible for a few drugs.
  - For the majority of drugs whose effect is not quantifiable, the plasma drug concentration remains the best marker of effect.
- For some drugs, we can link the parameters and equations of PK to those of PD, resulting in a PKPD model which can predict pharmacological effect over time.

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- Only that fraction of the administered dose which actually reaches the systemic circulation will be available to elicit a pharmacological effect.

- For an intravenous solution, the amount of drug that reaches general circulation is the dose administered.

$$\text{Dose} = X_0 = (\text{AUC})_0^{\infty} KV$$

...

- For the extravascular route, the amount of drug that reaches general circulation is the product of the bioavailable fraction (F) and the dose administered.

$$F \times \text{Dose} = FX_0 = (\text{AUC})_0^{\infty} KV$$

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- **Some important terms in Pharmacokinetics:**

Drug absorption

- Is the process of uptake of the compound from the site of application into the systemic circulation

Drug disposition

- Is the description of drug distribution and elimination, i.e., process after absorption.

Drug Accumulation

- Is the increase in drug concentration in blood and tissue upon multiple dosing until steady state is reached.

Steady state

- Is a level of drug accumulation in blood or tissue upon multiple dosing when input and output are at equilibrium.

- The steady state drug concentrations fluctuate between a maximum and a minimum steady state concentration within each dosing interval.

Biophase

- Is the actual site of action of drugs in the body.

Receptor

- Is the site in the biophase to which drug molecules can be bound.
- A receptor is usually a protein or proteinaceous material.

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Linear pharmacokinetics

- Directly proportional relationship between the observed plasma concentration and/or the amount of drug eliminated in the urine and the administered dose of the drug.

Nonlinear or saturation pharmacokinetics

- This refers to a change of one or more of the PK parameters during ADME by **saturation** or **overloading** of processes due to increased dose sizes.

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Chronopharmacokinetics

- The study of the **temporal change** of pharmacokinetic drug parameters.

LADMER system

- Processes of **liberation** of API, its **absorption**, **distribution** and **metabolism** in the body, its **elimination** from the body and the achievement of **response**.

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Dosage regimen

- The systematized dosage schedule for therapy, i.e., the proper dose sizes and proper dosing intervals required to produce clinical effectiveness or to maintain a therapeutic concentration in the body.

Loading dose, priming dose or initial dose

- The dose size used in initiating therapy so as to yield therapeutic concentrations which will result in clinical effectiveness.

Maintenance dose

- The dose required to maintain the clinical effectiveness or therapeutic concentration according to the dosage regimen.

Onset of action

- The time at which the administered drug reaches the therapeutic range and begins to produce the effect.

Duration of action

- The time span from the beginning of the onset of action up to the termination of action.

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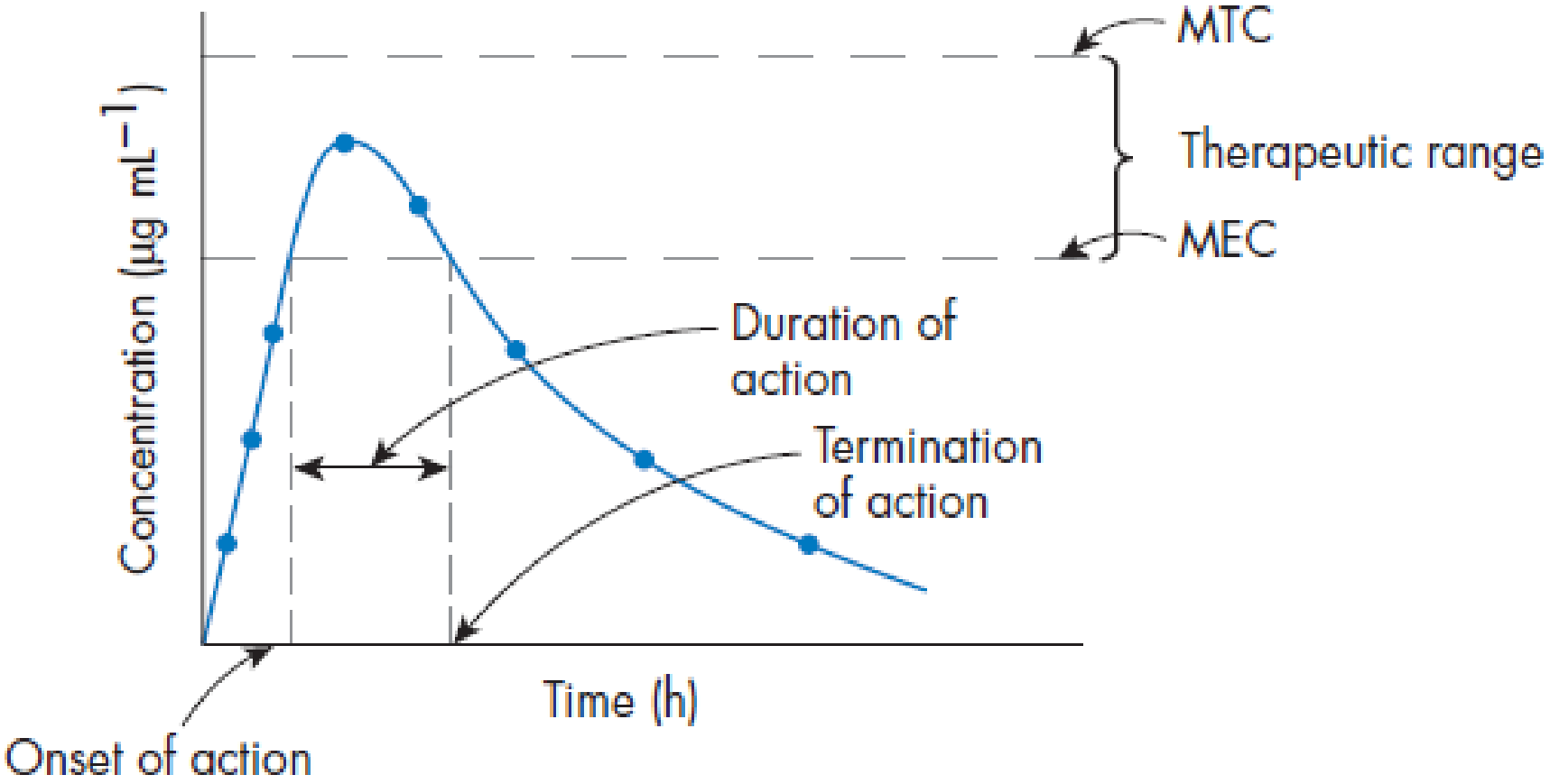
Termination of action

- The time at which the drug concentration in the plasma falls below the minimum effective concentration (MEC).

Therapeutic range

- The plasma concentration range within which the drug is likely to produce the therapeutic activity or effect.


MTC
Therapeutic range
MEC
Concentration (μg mL⁻¹)
Duration of action
Termination of action
Time (h)
Onset of action

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- **Pharmacokinetic parameters**

  Two categories:

  - **Qualitative or descriptive** - in that the parameters are observational, requiring no formula for calculation.

    - E.g., maximal observed concentration of a drug, amount of drug excreted in urine during a given time period.

  - **Quantitative** - that require a mathematical formalism for calculation.

    - E.g., mean residence times, clearance rates, volumes of distribution.